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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,484	11/28/2001	Yen Choo	8325-2004 G8-US1	2713
20855 7590 02/14/2007 ROBINS & PASTERNAK 1731 EMBARCADERO ROAD SUITE 230 PALO ALTO, CA 94303			EXAMINER SULLIVAN, DANIEL M	
			ART UNIT 1636	PAPER NUMBER
			MAIL DATE 02/14/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

09/996,484

Applicant(s)

CHOO ET AL.

Examiner

Daniel M. Sullivan

Art Unit

1636

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 01 February 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☒ The Notice of Appeal was filed on 01 February 2007. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).


4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: \_\_\_\_\_.  
Claim(s) withdrawn from consideration: \_\_\_\_\_.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
13. ☐ Other: \_\_\_\_\_.

  
Daniel M. Sullivan, Ph.D.  
Primary Examiner  
Art Unit: 1636

**Continuation of 11. does NOT place the application in condition for allowance because:**

In response to the rejection of claim 34 under 35 U.S.C. §102(b) as anticipated by Barbas et al., Applicant contends that the claim is not anticipated by the art because the heterodimers disclosed in Barbas et al. do not comprise a ligand. Rather the dimerization domains of Jun and Fos interact directly to form the heterodimer. This argument has been fully considered but is not deemed persuasive. As discussed in the Final Office action, “[T]he specification states at p. 49, ll. 1-2, ‘A ligand according to the invention is typically any molecule capable of binding to any of the other components of a switching system.’ Thus, the amended claim [which no longer requires that the polypeptides bind in a manner modulatable by a ligand] now embraces any complex comprising a heterodimer comprising a first and second DNA-binding polypeptide and anything that binds to either one of the first and second polypeptide...” (30 October 2006 Office Action, page 7.) As further stated at page 8 of the Final Office Action, “On page 1, ¶4, Barbas et al. teaches that zinc finger domains are folded around a zinc ion. As the zinc ion is bound to the first and second protein moieties, zinc is a ligand according to the broadest reasonable interpretation of the claim limitation.” Thus, the heterodimer of Barbas et al. does, in fact, comprise a ligand and anticipates every element of the claimed invention. Therefore, the claim is properly rejected under 35 U.S.C. §102(b) as anticipated by the art.

With regard to the rejection of claim 48 under 35 U.S.C. §103(a) as being unpatentable over Vegeto et al. WO 93/23431 as evidenced by McEwan et al. and Bledso et al. in view of Liu et al., Applicant contends that the art does not provide sufficient suggestion and motivation to combine the references. Applicant cites several court decisions relating to suggestion and motivation in obviousness rejections, and concludes that it is clear that the teachings of Vegeto and Liu do not support a finding of obviousness. Applicant contends that the Office has not pointed to anything in either reference or the art as a whole that would motivate the skilled artisan to modify Vegeto’s steroid receptor-containing, single DNA-binding domain, exogenous gene-regulating system to arrive at the subject matter of claim 48. Applicant contends that there is nothing in Vegeto that suggests the desirability of systems comprising two DNA-binding polypeptide components whose interaction is modulated by a ligand and Liu does not contain any suggestion of Cys<sub>2</sub>His<sub>2</sub> DNA binding domains.

At the outset, it is noted that the suggestion and motivation to combine references need not be explicitly stated in the references. “The teaching, suggestion, or motivation must be found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. ‘The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.’ *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).” MPEP 2143.01; emphasis added.

Furthermore, the Federal Circuit has recently clarified its position on the teaching, suggestion, motivation (TSM) test. In particular, in *Dystar Textilfarben v. C.H. Patrick*, 80 USPQ2d 1641 (Fed. Cir. 2006), the court states at pages 20-21:

Our suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense... Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the “improvement” is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical—we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references.

Thus, it is clear that the suggestion and motivation to combine references can be implicit, based on the knowledge of one of ordinary skill in the art and the nature of the problem to be solved as a whole, and requires consideration of common knowledge and common sense.

Suggestion and motivation to combine the teachings of Vegeto et al. and Liu et al. is more than adequately supported by the teachings found therein, common knowledge and common sense. As stated in the 18 April 2006 Office Action, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the molecular switch of Vegeto et al. to include the engineered polydactyl Cys2-His2 zinc finger DNA binding domain of Liu et al. Motivation to combine these teachings comes from the nature of the problem to be solved by the molecular switch of Vegeto et al., which is to regulate expression of a nucleic acid in mammals and from the teachings of Liu et al. that: a) specific delivery of a DNA-binding protein to a single site within a genome as complex as that found in humans, 3.5 billion bp, requires an address of at least 16 bp (p. 5525, bridging col. 1-2); b) although natural proteins containing long polydactyl arrays of zinc-finger domains have been inferred from sequence, no zinc finger proteins have been demonstrated to bind such a long contiguous DNA sequence (p. 5525, bridging col. 1-2); and c) the polydactyl proteins described therein can bind to a contiguous 18 bp DNA sequence with high affinity and specificity and function in human cells to activate or repress transcription. Viewed as a whole, the skilled artisan would clearly be motivated to substitute the polydactyl DNA binding domain of Liu et al. for the DNA binding domains contemplated by Vegeto et al. for construction of a molecular switch operative in mammalian cells to obtain the expected benefit of highly specific delivery of the switch in the complex mammalian genome.

Finally, Applicant contends that the combination of Vegeto et al. and Liu et al. would not result in the claimed polypeptides because Liu et al. in no way teaches two DNA-binding polypeptide,

where dimerization is mediated by a ligand and Vegeto is clear that the molecular switch includes either a steroid receptor DNA binding domain or a modified steroid receptor in which the DNA binding domain is replaced. Applicant further contends that the modification would render Vegeto unsatisfactory for its intended purpose.

This argument is not persuasive. As Applicant acknowledges, Vegeto et al. teaches a modified steroid receptor in which the native DNA binding domain is replaced and, as evidenced by McEwan et al. and Bledsoe et al., wherein dimerization is mediated by a ligand. The basis of the rejection is that it would be obvious to use the polydactyl DNA binding domain taught by Liu et al. in the modified steroid receptor taught by Vegeto et al. The rejection is based on the art considered as a whole; therefore, it is not necessary for Liu et al. to teach the elements supplied by Vegeto et al. and *vice versa*. With regard to the modification rendering the switch of Vegeto et al. unsatisfactory for its intended purpose, this argument was fully addressed in the 30 October 2006 Office Action at page 6. In brief, there is nothing of record that to suggest that the DNA binding domain taught by Liu et al. would render the switching system of Vegeto et al. unsuitable for its intended purpose.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claim stands rejected under 35 USC §103(a) as obvious over the art.